

WHAT IS CLAIMED IS:

1. A method of inhibiting zinc release from neurons, comprising:

providing to said neurons at least one agent that inhibits nitric oxide

5 synthesis; and

reducing levels of nitric oxide that induce release of zinc thereby inhibiting

release of zinc from said neurons.

2. The method of claim 1, wherein said zinc is located in presynaptic

10 vesicles, in post-synaptic zinc sequestering proteins, or in mitochondrial stores in post-synaptic neurons, or a combination thereof.

3. The method of claim 1, wherein said agent(s) inhibits the activity
of neuronal nitric oxide synthase, inducible nitric oxide synthase or a combination thereof.

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4. The method of claim 1, wherein said agent is 7-nitroindazole, S-methyl-1-thiocitrulline, the protein PIN, 2-amino-5,6-methyl-4H-1,3-thiazine, N(6)-iminoethyl-L-lysine, N(6)-iminoethyl-L-lysine, N-(3-aminomethyl)benzyl acetamidine, or S-[2-amino-(1-iminoethylamino)5-thioheptanoic acid].

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5. The method of claim 1, wherein inhibition of zinc release prevents
a zinc-mediated brain injury.

6. The method of claim 5, wherein said zinc-mediated brain injury is caused by stroke, head trauma, ischemia, seizure, or surgery compromising cerebral blood flow.

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7. A method of preventing zinc-mediated brain injury, comprising:
administering to an individual susceptible to trauma-induced excitotoxicity one or more first agent(s) that inhibits nitric oxide synthesis; and
reducing nitric oxide-induced release of zinc from neuronal cells in response
10 to said trauma-induced excitotoxicity thereby preventing zinc-mediated brain injury.

8. The method of claim 7, wherein said first agent inhibits nitric oxide synthetic activity of neuronal nitric oxide synthase, of inducible nitric oxide synthase, of both neuronal nitric oxide synthase and inducible nitric oxide synthase or a combination
15 thereof.

9. The method of claim 7, wherein said first agent is 7-nitroindazole, S-methyl-1-thiocitrulline, the protein PIN, 2-amino-5,6-methyl-4H-1,3-thiazine, N(6)-iminoethyl-L-lysine, N(6)-iminoethyl-L-lysine, N-(3-aminomethyl)benzyl acetamidine,
20 or S-[2-amino-(1-iminoethylamino)5-thioheptanoic acid].

10. The method of claim 7, further comprising:

administering a second agent to improve cerebral blood flow, said second agent different from said first agent(s).

11. The method of claim 10, wherein said second agent increases the
5 activity of endothelial nitric oxide synthase.

12. The method of claim 11, wherein said second agent is simvastatin,
17-beta-estradiol, a corticosteroid, endothelin, or AT2 receptor agonists.

10 13. The method of claim 12, wherein said corticosteroid is
dexamethasone.

14. The method of claim 10, wherein said second agent is a pressor.

15 15. The method of claim 14, wherein said pressor is dopamine,
vasopressin, angiotensin II, or epinephrine.

16. The method of claim 7, wherein release of said excitotoxic zinc is
caused by stroke, head trauma, ischemia, seizure, or surgery compromising cerebral blood
20 flow.

17. The method of claim 16, wherein said surgery is cardiaobypass, cardiopulmonary bypass or carotid endarterectomy.

18. The method of claim 7, wherein said excitotoxic zinc is released
5 from presynaptic vesicles, post-synaptic zinc sequestering proteins or mitochondrial stores in the post-synaptic neurons.

19. The method of claim 7, wherein said agent(s) is administered in a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

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20. A method of improving cerebral blood flow while preventing zinc-mediated brain injury in an individual in need of such therapeutic intervention, comprising:

administering to said individual an agent(s) that inhibits one of or both of
15 neuronal nitric oxide synthase and inducible nitric oxide synthase, and

administering an agent that increases the activity of endothelial nitric oxide synthase;

wherein the combination of said agents modulates nitric oxide synthesis in said individual such that the nitric oxide synthesized improves cerebral blood flow, but
20 said nitric oxide does not induce release of neurotoxic amounts of zinc thereby preventing zinc-mediated brain injury.

21. The method of claim 20, wherein said agent inhibiting nNOS or iNOS is 7-nitroindazole, S-methyl-1-thiocitrulline, the protein PIN, 2-amino-5,6-methyl-4H-1,3-thiazine, N(6)-iminoethyl-L-lysine, N(6)-iminoethyl-L-lysine, N-(3-aminomethyl)benzyl acetamidine, or S-[2-amino-(1-iminoethylamino)5-thioheptanoic acid].

22. The method of claim 20, wherein said agent increasing the activity of eNOS is simvastatin, 17-beta-estradiol, a corticosteroid, endothelin, or AT2 receptor agonists.

23. The method of claim 22, wherein said corticosteroid is dexamethasone.

24. The method of claim 20, wherein said zinc-mediated brain injury is caused by stroke, head trauma, ischemia, seizure, or surgery that would compromise cerebral blood flow.

25. The method of claim 24, wherein said surgery is cardiaobypass, cardiopulmonary bypass or carotid endarterectomy.

26. The method of claim 20, wherein said neurotoxic zinc is released from presynaptic vesicles, post-synaptic zinc sequestering proteins or mitochondrial stores in the post-synaptic neurons.

5 27. The method of claim 20, wherein said agents are administered in a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

28. A method of improving cerebral blood flow while preventing zinc-mediated brain injury in an individual in need of such therapeutic intervention,
10 comprising:

administering to said individual an agent(s) that inhibits one of or both of neuronal nitric oxide synthase and inducible nitric oxide synthase; and in combination

administering a pressor;

wherein said pressor improves cerebral blood flow as said agent(s) reduces
15 nitric oxide-induced release of neurotoxic zinc thereby preventing zinc-mediated brain injury.

29. The method of claim 28, wherein said agent inhibiting nNOS or iNOS is 7-nitroindazole, S-methyl-1-thiocitrulline (SMTC), the protein PIN, 2-amino-
20 5,6-methyl-4H-1,3-thiazine, N(6)-iminoethyl-L-lysine, N(6)-iminoethyl-L-lysine, N-(3-aminomethyl)benzyl acetamidine, or S-[2-amino-(1-iminoethylamino)5-thioheptanoic acid].

30. The method of claim 28, wherein said pressor is dopamine, vasopressin, angiotensin II, or epinephrine.

5 31. The method of claim 28, wherein said zinc-mediated brain injury is caused by stroke, head trauma, ischemia, seizure, or surgery that would compromise cerebral blood flow.

32. The method of claim 31, wherein said surgery is cardiobypass, 10 cardiopulmonary bypass or carotid endarterectomy.

33. The method of claim 28, wherein said neurotoxic zinc is released from presynaptic vesicles, post-synaptic zinc sequestering proteins or mitochondrial stores in the post-synaptic neurons.

15 34. The method of claim 28, wherein said agent(s) and said pressor are administered in a pharmaceutical composition comprising a pharmaceutically acceptable carrier.